Published in final edited form as:
J Thorac Cardiovasc Surg. 2010 December ; 140(6 Suppl): S2–S51. doi:10.1016/j.jtcvs.2010.07.027.

Treatment guidelines for thoracic aortic aneurysms and dissections based on the underlying causative gene

Dianna M. Milewicz, MD, PhD, **Ellen S. Regalado, MS**, and **Dong-chuan Guo, PhD**
Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX

Thoracic aortic aneurysms leading to acute aortic dissections (TAAD) are a common cause of premature death in the United States.[1,2] The natural history of ascending aortic aneurysms is to progressively enlarge over time and ultimately lead to life-threatening acute aortic dissection or aortic rupture. Although medical treatments can slow the enlargement of ascending aortic aneurysms, the mainstay of prevention of aortic dissection is surgical repair when the aortic diameter expands to 5.5 cm or more.[2] However, aortic dissections occur in some patients who have little or no aortic enlargement. In fact, data from the International Registry of Aortic Dissections (IRAD) indicate that nearly 60% of aneurysms dissect at aortic diameters < 5.5 cm.[3] Because approximately one-half of patients with acute ascending aortic dissection die suddenly without reaching a hospital, preventing premature deaths necessitates identifying individuals at risk for aortic dissection, carefully monitoring the diameter of the ascending aorta, and performing timely elective surgical repair. Therefore, improved clinical predictors are needed not only to identify who is at risk for TAAD, but also to determine the aortic diameter that justifies the risk of surgical repair of a thoracic aortic aneurysm to prevent an acute aortic dissection.

Hypertension and the presence of a congenital bicuspid aortic valve (BAV) are risk factors for the disease, but a genetic predisposition also plays a prominent role in the etiology.[2] For many years it has been known that patients with Marfan syndrome (MFS), an autosomal dominant syndrome with skeletal and ocular features, are highly predisposed to TAAD.[4] MFS results from mutations in *FBN1*, which encodes fibrillin-1, a component of elastin-associated microfibrils.[5] Loeys-Dietz syndrome (LDS) also predisposes patients to TAAD, along with craniofacial abnormalities, skeletal features of MFS, arterial tortuosity, and aneurysms and dissections of other arteries.[6,7] Arterial involvement beyond the ascending aorta is widespread, but primarily involves the thoracic arterial circulation, including the coronary, subclavian, pulmonary, and intercostal arteries, and surgical intervention is generally successful.[8] LDS results from mutations in either the transforming growth factor-beta receptor type I or II genes (*TGFBR1* or *TGFBR2*).

Clinical studies of MFS and LDS have provided the first evidence that the timing of surgical repair of thoracic aortic aneurysms can be dictated by the underlying mutated gene causing the disease. Both syndromes lead to aneurysms involving the aortic root (defined as the segment of the ascending aorta extending from the valvular annulus to the sinotubular junction and including the sinuses of Valsalva). MFS patients with *FBN1* mutations are at a

Corresponding Author: Dianna M. Milewicz, M.D., Ph.D., The University of Texas Health Science Center at Houston, 6431 Fannin, MSB 6.100, Houston, TX 77030, Phone: 713-500-6715, Fax: 713-500-0693, Dianna.M.Milewicz@uth.tmc.edu.

low risk for acute dissections until the aorta is greater than 5.5 cm in diameter.[9] In contrast, accumulating data from our research and others suggest that patients with a *TGFBR2* mutation (either LDS or FTAAD patients as described below) experience aortic dissections with little to no enlargement of the aorta, leading to the recommendation that patients with a *TGFBR2* mutation undergo surgical repair of an aortic aneurysm when the diameter reaches 4.2 cm.[2] In addition to determining the risk of aortic dissection at a given diameter, current data suggest that the underlying mutation also dictates the risk for further vascular disease beyond the ascending thoracic aorta. For example, patients with *TGFBR2* mutations are at a high risk for aneurysms and dissections beyond the aortic root, including cerebrovascular disease,[7,10] whereas the risk for involvement of other arteries is low in patients with MFS.

We and others have determined that up to 19% of TAAD patients without a genetic syndrome have a family history of TAAD (FTAAD), indicating a significant genetic component to this disease.[11,12] FTAAD is primarily inherited in families as an autosomal dominant condition with decreased penetrance, primarily in women.[12,13] The familial aortic disease is variable in its expression of thoracic aortic disease, including varying age of disease onset, severity of presentation, and whether the aortic aneurysm involves the aortic root or the ascending aorta, sparing the root. There is interfamilial variability in FTAAD, with a subset of families with members who experience aortic dissections with little to no enlargement of the ascending aorta (e.g., family TAA008).[13] Additionally, variability in these families is evident in the clinical features that are associated with or segregate with the thoracic aortic disease in family members, which can include intracranial aneurysms (ICAs), iliac and popliteal artery aneurysms, occlusive vascular diseases (early onset stroke and coronary artery disease), abdominal aortic aneurysms (AAAs), and patent ductus arteriosus (PDA).[14,15]

We have identified *TGFBR1* and *TGFBR2* mutations in approximately 3 – 5% of FTAAD families whose members do not have features of LDS, suggesting a similar pathogenesis for disease in these FTAAD families.[8,16,17] In FTAAD families with *TGFBR2* mutations, aortic dissections occur with minimal enlargement of the aortic root. Therefore, the recommendation for surgical repair of an aortic aneurysm when the diameter reaches 4.2 cm applies to both LDS and FTAAD patients. Interestingly, FTAAD can result from mutations in either *TGFBR1* or *TGFBR2,* but data are emerging in these families to support the notion that there are differences in vascular disease presentation and risk for dissection based on whether *TGFBR1* or *TGFBR2* is the causative gene.[10]

We and others have begun to identify additional genes for FTAAD. We have determined that the most frequently mutated gene is the smooth muscle cell (SMC)-specific isoform of α-actin, *ACTA2*, which is responsible for 10-14% of familial thoracic aortic disease.[15] A large French family was used by other investigators to map and identify mutations in the SMC-specific isoform of β-myosin heavy chain, *MYH11*.[18] These genes encode the major proteins found in SMC contractile units that function to contract the SMC to withstand the stress of pulsatile blood flow, and regulate flow and pressure. We have hypothesized that proper SMC contraction is implicated in maintaining the structural integrity of the ascending aorta, with disruption of SMC contractile function leading to TAAD.[19]

Analysis of thoracic aortic disease in *ACTA2* mutation patients reveals some clinical features of the disease. The penetrance of TAAD in individuals with *ACTA2* mutations is approximately 50%, i.e. half of the *ACTA2* mutation carriers do not have thoracic aortic disease. The low penetrance of *ACTA2* mutations differs from what is observed at other identified loci and genes for FTAAD, with an age-related penetrance that is higher.[16,20] The majority of the *ACTA2* FTAAD individuals presented with acute ascending (type A) or descending (type B) aortic dissections, and 16 of the 24 deaths were due to type A

dissections**.** Two individuals experienced type A dissections at documented ascending aortic diameters of 4.5 and 4.6 cm, whereas 11 individuals dissected at aortic diameters greater than 5.0 cm. Aortic dissections occurred in 3 individuals under 20 years of age, and two women died of dissections post partum. Three young men had type B dissections complicated by rupture or aneurysm formation at 13, 16 and 21 years of age. Finally, a rare patient with *ACTA2* mutation can present with BAV or PDA.

Investigations into other vascular disease beyond thoracic aortic disease revealed that *ACTA2* mutations predispose not only to TAAD but also to occlusive vascular diseases, including early onset coronary artery disease, stroke, and Moyamoya disease (a rare stroke syndrome).[21] An investigation into occlusive vascular diseases in FTAAD patients with *ACTA2* mutations was initiated when we observed that all mutation carriers in a family had livedo reticularis--,a skin rash due to occlusion of the dermal arteries--whether or not they had aortic disease.[15] Additionally, we noted that vasa vasorum in the aortas of *ACTA2* mutation patients were occluded due to SMC proliferation. Subsequent linkage and association studies confirmed that *ACTA2* mutations also cause occlusive vascular diseases, such as CAD and stroke, before the age of 55 years in men and 60 years in women. Moreover, a subset of *ACTA2* mutations also predispose to Moyamoya disease, a rare cerebrovascular syndrome characterized by bilateral occlusion or stenosis of the terminal internal carotid arteries, and the formation of collateral vessel networks at the base of the brain, so-called “Moyamoya vessels”.[22,23] These data demonstrate that diffuse vascular disease resulting from either occluded or dilated arteries can be caused by a mutation in a single gene, and have direct implications for clinical management of *ACTA2* mutation patients.

MYH11 mutations are a rare cause of familial TAAD, and only occur in families where one or more members with TAAD also have PDA.[18,24,25] Limited data of thoracic aortic disease in patients with *MYH11* mutations suggest that these patients have aneurysms involving the ascending aorta, and can experience aortic dissections with aortic diameters of 4.4 cm.[25]

Since fewer than 20% of FTAAD families have mutations in one of the known genes, specific management for the majority of FTAAD families is still not defined. For these families, we recommend that the aortic disease presentation in the affected family members be assessed, along with other vascular disease or clinical features, and the management be based on this assessment. If family members have experienced dissections at aortic diameters less than 5.0 cm, then surgical repair for other affected family membersat diameters below 5.0 cm should be considered. In families with TAAD associated with BAV, studies have indicated that the component features--BAV and TAAD--are independent manifestations of a single gene defect.[14] Therefore, family members need to have routine aortic imaging whether or not BAV is present.

In summary, as novel FTAAD genes are discovered, clinical features associated with each gene are identified that inform the clinical management of patients based on the underlying gene mutation. Based on these findings, we are recommending that if the underlying gene causing the predisposition to thoracic aortic disease is identified in a patient or family, the management of the aortic disease and risk for additional vascular diseases be based on the causative gene.

Acknowledgments

This work was support by the National Institutes of Health P50HL083794-01 (D.M.M.), RO1 HL62594 (D.M.M.), R21 HL091509, and Doris Duke Charitable Trust.

Reference List

1. Hoyert DL, Arias E, Smith BL, Murphy SL, Kochanek KD. Deaths: final data for 1999. Natl Vital Stat Rep. 2001; 49:1–113.
2. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr. et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease: Executive Summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010
3. Pape LA, Tsai TT, Isselbacher EM, Oh JK, Gara PT, Evangelista A, et al. Aortic diameter >or = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation. 2007; 116:1120–7. [PubMed: 17709637]
4. Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. N Engl J Med. 1979; 300:772–7. [PubMed: 370588]
5. Dietz HC, Pyeritz RE. Mutations in the human gene for fibrillin-1 (FBN1) in the Marfan syndrome and related disorders. Hum Mol Genet. 1995; 4 Spec No:1799-809.
6. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005
7. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006; 355:788–98. [PubMed: 16928994]
8. LeMaire SA, Pannu H, Tran-Fadulu V, Carter SA, Coselli JS, Milewicz DM. Severe aortic and arterial aneurysms associated with a TGFBR2 mutation. Nat Clin Pract Cardiovasc Med. 2007; 4:167–71. [PubMed: 17330129]
9. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. Circulation. 2005; 111:e150–e157. [PubMed: 15781745]
10. Tran-Fadulu VT, Pannu H, Kim DH, Vick GW III, Lonsford CM, Lafont AL, et al. Analysis of Multigenerational Families with Thoracic Aortic Aneurysms and Dissections Due to TGFBR1 or TGFBR2 Mutations. J Med Genet. 2009; 46:607–13. [PubMed: 19542084]
11. Biddinger A, Rocklin M, Coselli J, Milewicz DM. Familial thoracic aortic dilatations and dissections: a case control study. J Vasc Surg. 1997; 25:506–11. [PubMed: 9081132]
12. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA, et al. Familial thoracic aortic aneurysms and dissections--incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg. 2006; 82:1400–5. [PubMed: 16996941]
13. Milewicz DM, Chen H, Park ES, Petty EM, Zaghi H, Shashidhar G, et al. Reduced penetrance and variable expressivity of familial thoracic aortic aneurysms/dissections. Am J Cardiol. 1998; 82:474–9. [PubMed: 9723636]
14. Loscalzo ML, Goh DL, Loeys B, Kent KC, Spevak PJ, Dietz HC. Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. Am J Med Genet A. 2007; 143:1960–7. [PubMed: 17676603]
15. Guo DC, Pannu H, Papke CL, Yu RK, Avidan N, Bourgeois S, et al. Mutations in smooth muscle alpha-actin (*ACTA2*) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007; 39:1488–93. [PubMed: 17994018]
16. Pannu H, Fadulu V, Chang J, Lafont A, Hasham SN, Sparks E, et al. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. Circulation. 2005; 112:513–20. [PubMed: 16027248]
17. Tran-Fadulu V, Pannu H, Kim DH, Vick GW III, Lonsford CM, Lafont AL, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. J Med Genet. 2009; 46:607–13. [PubMed: 19542084]

18. Zhu L, Vranckx R, Khau Van KP, Lalande A, Boisset N, Mathieu F, et al. Mutations in myosin heavy chain 11 cause a syndrome associating thoracic aortic aneurysm/aortic dissection and patent ductus arteriosus. Nat Genet. 2006; 38:343–9. [PubMed: 16444274]

19. Milewicz DM, Guo D, Fadulu V, Lafont A, Papke C, Inamoto S, et al. Genetic Basis of Thoracic Aortic Aneurysms and Dissections: Focus on Smooth Muscle Cell Contractile Dysfunction. Annu Rev Genomics Hum Genet. 2008; 9:283–302. [PubMed: 18544034]

20. Guo D, Hasham S, Kuang SQ, Vaughan CJ, Boerwinkle E, Chen H, et al. Familial thoracic aortic aneurysms and dissections: genetic heterogeneity with a major locus mapping to 5q13-14. Circulation. 2001; 103:2461–8. [PubMed: 11369686]

21. Guo DC, Papke CL, Tran-Fadulu V, Regalado ES, Avidan N, Johnson RJ, et al. Mutations in smooth muscle alpha-actin (ACTA2) cause coronary artery disease, stroke, and moyamoya disease, along with thoracic aortic disease. Am J Hum Genet. 2009; 84:617–27. [PubMed: 19409525]

22. Kudo T. Spontaneous occlusion of the circle of Willis. A disease apparently confined to Japanese. Neurology. 1968; 18:485–96. [PubMed: 5691175]

23. Milewicz DM, Kwartler CS, Papke CL, Regalado ES, Cao J, Reid AJ. Genetic variants promoting smooth muscle cell proliferation can result in diffuse and diverse vascular diseases: evidence for a hyperplastic vasculomyopathy. Genet Med. 2010; 12:196–203. [PubMed: 20130469]

24. Van Kien PK, Mathieu F, Zhu L, Lalande A, Betard C, Lathrop M, et al. Mapping of familial thoracic aortic aneurysm/dissection with patent ductus arteriosus to 16p12.2-p13.13. Circulation. 2005; 112:200–6. [PubMed: 15998682]

25. Pannu H, Tran-Fadulu V, Papke CL, Scherer S, Liu Y, Presley C, et al. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. Hum Mol Genet. 2007; 16:3453–62.